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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,885	01/25/2006	Juan Lopez De Silanes	23990080000JAGLAV	8053

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EXAMINER	
SKELDING, ZACHARY S	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,885	LOPEZ DE SILANES ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-61* is/are pending in the application.

4a) Of the above claim(s) *22,23,25,28,30 and 37-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20, 21, 24, 26, 27, 29 and 31-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-16-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse filed May 7, 2008 is acknowledged.

   Claims 1-19 have been canceled.

   Claims 20-61 are pending.

2. Applicant's election with traverse of Group I and the species "corneal transplant rejection" in the reply filed on May 7, 2008 is acknowledged. The traversal is on the ground(s) that Groups I and IX possess unity of invention because they both rely on the same special technical feature of anti-TNFα Fab'2; because U.S. 6,270,766 is insufficient to break unity of invention since, "[t]he reference does not actually describe administration of the chimeric anti-TNF antibodies *via* a topical administration route, but instead discloses a general laundry list of various administration routes without providing any teaching of how to accomplish this task. The ordinary artisan reading the '766 patent could not have predictably arrived at a method of topically administering anti-cytokine F(ab')2 antibody fragments given the teachings of the reference"; and because the species of invention share the property that they all involve a cytokine mediated immune response and a search for one would find art for the others.

   This is not found persuasive essentially for the reasons of record put forth in the Restriction Requirement mailed April 7, 2008.

   In short, with respect to Groups I and IX, these Groups do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the inventions of Groups I-X do not share a special technical feature that defines a contribution over the prior art of Feldman et al., U.S. Patent No. 6270766.

   In particular, Feldman teaches a method of treating rheumatoid arthritis by topically administering anti-TNFα F(ab')2 antibody fragments (see Feldman column 12, 1st paragraph, column 18, 2nd paragraph and claim 1).

   With respect to applicant's arguments about the teachings of Feldman, Feldman need not provide a working example of the "administration of the chimeric anti-TNF antibodies *via* a topical administration route" in order to demonstrate that the claimed invention lacks unity. Feldman merely needs to teach the elements of the claimed invention either explicitly, or inherently, and to provide sufficient description of the invention for a person of ordinary skill in the art to carry out the claimed invention. Feldman meets these requirements for the reasons given above.

   As stated in MPEP § 2123, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned.

They are part of the literature of the art, relevant for all they contain." In re Heck, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting In re Lemelson, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

Also, a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989).

With respect to applicant's argument about the species election requirement, applicant's argument is not found convincing because the species of invention lack unity for the same reasons that the Groups of inventions lack unity and further because applicant has provided no objective evidence that a search of the species would not be unduly burdensome for the reasons of record.

The requirement is still deemed proper and is therefore made FINAL.

Thus, claims 20, 21, 24, 26, 27, 29 and 31-36 are under consideration as they read on a method for treating a cytokine-mediated immune reaction in a patient in need thereof comprising, topically administering to said patient an effective amount of anti-cytokine F(ab')2 antibody fragments, wherein said cytokine is TNFα and wherein the species of disorder is "corneal transplant rejection".

Accordingly, claims 22, 23, 25, 28, 30, and 37-61 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group or species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 7, 2008.

3. Claim 36 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, claim 36 has not been further treated on the merits.

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 21, 24, 26, 27, 29 lack proper antecedent basis in the specification. Furthermore, while the subject matter of claim 31 which is "rejection of...tissue transplant" has proper antecedent basis in the specification, "rejection of a prosthetic" lacks antecedent basis in the specification.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 20, 21, 24, 26, 27, 29, 31 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421).

Pluenneke teaches a method of treating corneal transplant rejection with anti-TNFα antibody such as the antibodies described in EP 0 516 785 and EP 0 492 448 (see Pluenneke, in particular, paragraphs [0032] and [0071]). Pluenneke further teaches that TNFα antagonists may be administered via eyedrops (see Pluenneke, in particular, paragraphs [0026]). Pluenneke teaches that the anti-TNFα antagonist should be administered in the form of a physiologically acceptable composition, such as a saline buffered solution (see Pluenneke, in particular, page 4, paragraph [0027]).

Pluenneke differs from the claimed invention in that Pluenneke does not explicitly teach the use of an "$F(ab')_2$" anti-TNFα antibody fragment, or that the administered antibody be substantially free of albumin, whole antibodies, pyrogens and/or viruses.

However, it has long been known to one of ordinary skill in the art that $F(ab')_2$ antibody fragments, including $F(ab')_2$ anti-TNFα antibody fragments in particular, can effectively neutralize their target antigen, such as TNFα, while at the same time being less immunogenic in a human patient than an intact non-human antibody, easier to grown in microbial cells than an intact antibody, and have better tissue penetration than intact antibodies.

For example, Fabrizio teaches "The term 'antibody' is also meant to include intact molecules as well as fragments thereof, such as F_v, Fab and $F(ab')_2$, which are capable of binding antigen. Fab and $F(ab')_2$ fragments lack the Fc fragment of antibody, clear more rapidly from the circulation and may have less non specific tissue binding than intact antibody. It will be appreciated that F_v, Fab and $F(ab')_2$ and other fragments of the monoclonal antibody of the present invention may be used as well as the intact antibody for the same purposes, e.g. the detection of TNFα and treatment of those disease states in which TNFα has been shown to play a detrimental role." (see Fabrizio, page 5, 1st paragraph and claim 6).

While antigen-binding antibody fragments clear more rapidly from the circulation than do their larger brethren as described by Fabrizio above, it is also common knowledge in the art that due to their smaller size and lack of an Fc region F(ab')2 have better tissue penetrating ability than intact antibodies as taught by Horwitz with respect to heterodimeric $F(ab')_2$ fragments in particular: "The heterodimeric $F(ab')_2$ are preferred over known bispecific antibodies in their properties of a smaller molecular weight and the deletion of the Fc region, which can be advantageous when better tissue penetration and minimization of Fc-receptor cell interactions are desired." (See Horwitz paragraph bridging pages 15-16).

Horwitz further teaches a microbial based expression system for $F(ab')_2$ which enables the expression of antigen-binding antibody fragments such as $F(ab')_2$ directly from bacteria or yeast thereby allowing for the production of these antibody fragments without having the complications of incomplete proteolysis or nicking associated with traditional proteolytic means for making such antigen-binding antibody fragments (see page 5, 1st paragraph).

The teachings of Adair, another patent referenced by Pluenneke for its teaching of anti-TNFα antibodies suitable for treating, inter alia, corneal allograft rejection, echoes those of Fabrizio and Horwitz concerning the use of anti-TNFα antibodies to treat TNFα mediated inflammation and microbial production, respectively (see Adair, page 6, 1st paragraph and paragraph bridging pages 6-7).

Given the reference teachings, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat corneal allograft rejection with an $F(ab')_2$ fragment of an anti-TNFα antibody since such fragments have a number of generally useful features such as their ease of production and low immunogenicity (relative to intact non-human antibodies), and TNFα antagonistic activities equivalent to intact antibodies, as well as a specifically useful ability to penetrate tissues which could help in gaining access to the inner eye so as to neutralize TNFα where it is inducing inflammation subsequent to corneal transplantation.

One of ordinary skill in the art would have had a reasonable expectation of success in treating corneal allograft rejection via topical administration of a TNFα antagonist, such as an anti-TNF $F(ab')_2$, not only in view of the teachings of Pluenneke but also given the successful treatment of murine corneal allograft rejection via topical administration of a different TNFα antagonist, soluble TNF receptor I (see Reza Dana, in particular, Figures 3 and 6; page 9, 1st paragraph; the paragraph bridging pages 12-13).

With respect to the claimed limitation, "wherein said anti-cytokine $F(ab')_2$ antibody fragments are substantially free of albumin…," there does not appear to be any disclosure in the reference teachings that pharmaceutical compositions of $F(ab')_2$ antibody fragments suitable for administration to an animal or human must contain albumin, see for example, Adair page 7; Fabrizio, page 16, Section 10; Pluenneke, page 4, paragraph [0027]; Reza Dana, paragraph bridging pages 5-6.

Furthermore, with respect to the claimed limitation, "wherein said anti-cytokine $F(ab')_2$ antibody fragments are substantially free of …whole antibodies" it would have been obvious to one of ordinary skill in the art to ensure the presence of only $F(ab')_2$ antibodies when preparing a composition of anti-cytokine $F(ab')_2$ antibody for treating a cytokine mediated immune reaction in a patient using, for example, the methods taught by Horwitz.

Furthermore, with respect to the claimed limitation, "wherein said anti-cytokine $F(ab')_2$ antibody fragments are substantially free of …pyrogens and/or viruses," it has long been known to one of ordinary skill in the art that antibody preparations to be administered to

humans must be prepared in a manner such that the final product is substantially free of pyrogens and/or viruses.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana.

7. Claim 20, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421) as applied to claims 20, 21, 24, 26, 27, 29, 31 and 33-35 in Section 5 above,

and further in view of Zhu et al., (J Interferon Cytokine Res. 1999 Jun;19(6):661-9) and the instant specification at page 5, 1st paragraph.

The teachings of Pluenneke, Fabrizio, Horwitz, Adair and Reza Dana are given in Section 5 above.

The reference teachings differ from the claimed invention in that they do not explicitly teach a method of treating *acute* corneal allograft rejection.

However, Zhu teaches that in the murine model of corneal allograft rejection disclosed in the patent publication of Reza Dana TNFα is specifically overexpressed in allograft recipients during the early postoperative period, i.e., by the two week mark and prior to full expression of the immune response/profound stromal edema that occurs during graft rejection in this model (see Zhu, in particular page 667, left column, 1st paragraph).

In this regard, it is further noted that the characterization of the teachings of Zhu given the preceding paragraph is consistent with the teachings of the instant specification at page 5, 1st paragraph which refers to the Zhu publication in the context of disclosing a role for TNFα in acute corneal allograft rejection.

Given the teachings of Zhu, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have had a reasonable expectation of success in treating acute corneal allograft rejection with an $F(ab')_2$ anti-TNFα antibody since TNFα seems to be overexpressed well before even the earliest corneal graft rejection occurs in a model system.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Pluenneke, Fabrizio, Horwitz, Adair, Reza Dana, Zhu and the instant specification at page 5, 1st paragraph.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
August 19, 2008

/Michail A Belyavskyi/
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